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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/745,506	LAL ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *23-41 and 43-45* is/are pending in the application.

4a) Of the above claim(s) *23,24,34-38 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *25-33, 39, 41, 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 25-29, 31 and 32 have been amended. Claims 44 and 45 have been added. Claims 23-41, 43-45 are pending. Claims 23, 24, 34-38 and 40 remain withdrawn from consideration. Claims 25-33, 39, 41 and 43-45 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The rejection of claims 25-33, 39, 41, and 43 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility is maintained for reasons of record. New claims 44 and 45 are also rejected for the same reasons of record as set forth below.

The instant claims are drawn to the polynucleotide of SEQ ID NO:74 and the polynucleotides encoding SEQ ID NO:37. The instant application has provided a description of isolated polynucleotides encoding proteins and the proteins encoded thereby. The specification has collectively termed these proteins "NHRP". The instant application does not disclose the biological role for the NHRP protein of SEQ ID NO:37 or its significance. The instant specification asserts that it provides compositions which are useful in the diagnosis, prevention and treatment of diseases associated with cell proliferation, particularly immune responses and cancers (page 6, lines 1-4). The specification asserts that in cancers or immune disorders where NHRP is an "activator, transcription factor, enhancer, is being expressed, and is promoting cell proliferation; it is desirable to decrease the expression of NHRP" (page 44, lines 11-14). In cases where NHRP is an inhibitor or suppressor and not controlling cell proliferation it is desirable to provide the NHRP protein or increase the expression of NHRP (page 44, lines 14-16). The specification asserts that administration of NHRP of fragments thereof can be used to treat cancers such as "adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma", which include but are not limited to cancers of the "adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus" (page 44, lines 17-23). The specification asserts that antagonist which decrease the activity of NHRP may be administered to prevent or treat "AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, Graves disease, hyper eosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections and trauma". The specification also asserts that administration of an antagonist of NHRP could treat or prevent cancers such as "adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma and particularly cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus" (page 44 line 29 to page 45 line 22).

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the NHRP proteins, or the specific NHRP protein of SEQ ID NO:37. The disclosed protein of SEQ ID NO:37 is purported to have a potential function based upon the association

of the polynucleotide with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses (page 32, lines 24-30). After further research, a specific and substantial credible utility might be found for the claimed isolated polynucleotides. This further characterization, however, is part of the act of invention and until it has been undertaken the claimed invention is incomplete.

The specification states that the polynucleotides encoding the NHRP of the instant invention may be used for the diagnosis of conditions or diseases which are associated with expression of NHRP such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma and cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and immune disorders such as AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, Graves disease, hyper eosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and thyroiditis (page 56, lines 2-15).

In order for a polynucleotide to be useful for diagnosis of a disease, as asserted, there must be a well-established or disclosed correlation between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in inflamed tissues or in tissues derived from cancerous cells is not sufficient for establishing a utility for the diagnosis of disease absent information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern or evidence of altered form that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know that the claimed polynucleotide is either present only in diseased tissue to the exclusion of normal tissue, or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained in an effort to establish a differential expression pattern would constitute further research on the polynucleotide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696.

The instant claims are drawn to a protein of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that SEQ ID NO:37 or the polynucleotides encoding SEQ ID NO:37 of the instant application was, as of the filing date, useful for diagnosis, prevention and treatment of proliferation or immune response disorders or cancers, as stated above. Until some actual and specific significance can be attributed to the protein identified in the specification as SEQ ID NO:37, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

4. The rejection of claims 25-33, 39, 41 and 43 under 35 U.S.C. 112, first paragraph is maintained for reasons of record. New claims 44 and 45 are also rejected for the same reasons of record. Specifically, since the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant has submitted the Bedilion Declaration in order to provide persuasive evidence that the instant invention possesses patentable utility. Applicant argues that the Bedilion Declaration describes some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Applicant states that the Bedilion

declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Applicant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO:74 would be a more useful tool than microarrays lacking the same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and developmental disorders for such purposes as evaluating their efficacy and toxicity. This is not found to be persuasive Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. Also, the assertion that the claimed inventions "uses", as opposed to its function, is the subject of a proper analysis under the utility requirement, does render the asserted utility specific, since the specification has not establishes that the NHRP of SEQ ID NO:37, or the encoding polynucleotide of SEQ ID NO:74 is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that NHRP is expressed in at altered levels or forms in tissues exhibiting a pathological state. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases states which correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is also not substantial.

Applicant argues that the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function is without merit. However, Applicant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, in the case of a hypothetical specification disclosing that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. ∞ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker without the disclosure of the biological activity of the polypeptide encoded by the polynucleotide. However, such is not the fact pattern here. As stated in the previous Office action "The presence of a polynucleotide in inflamed tissues or in tissues derived from cancer cells is not sufficient for establishing a utility for the diagnosis of disease absent information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know that the claimed polynucleotide is either present only in diseased tissue to the exclusion of normal tissue, or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained in an effort to establish a differential expression pattern would constitute further research on the polynucleotide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696."

The instant specification discloses that the claimed polynucleotides encode SEQ ID NO:37 which is a human regulatory protein (page 17, line 19) which is related by sequence homology to a S cerevisiae protein sequence: GI 1322869. It is noted that neither the specification or any art of record has identified a specific and substantial utility, function or biological significance of said S cerevisae protein. On the basis of the observation that the claimed polynucleotides can be found in inflamed or cancerous tissues, the specification hypothesizes that the claimed polynucleotides are involved in the cancerous or inflamed states, but the expression of the polynucleotides or polypeptide encoded therefrom in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. There is no disclosure of a specific gene which is regulated by the polynucleotides or polypeptide of the NHRP of the instant invention. It is noted that the instant application is claiming a priority date of June 6, 1997 No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue, or a gene which is regulated by the instant NHRP. Also, no evidence has been brought forth that the claimed polynucleotides encode polypeptides having a specific human regulatory activity.

Applicants argue at pages 13-17 of the response that the use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Applicant states that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicant asserts that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor; because these methods can be carried out with any orphan receptor the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Applicant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Applicant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of cell proliferative and developmental. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific cell proliferative or developmental disorder. The specification merely discloses that the claimed polynucleotides are predicted to encode a protein which has sequence homolog to a S cerevisiae protein, and that they are expected to be involved in cancerous and inflammatory processes. The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology.

Beginning on the first paragraph of page 14 of the response, Applicant refers to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a useful tool in connection with conducting gene expression monitoring studies in connection with the development of new drugs for the treatment of immune responses and cancers, and that a person skilled in the art would request specifically that any DNA microarrray being used for such purposes would contain the polynucleotide of SEQ ID NO:74. Again, this is not found to be persuasive, because the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. The examiner does not contest the fact that DNA microarrays have utility as a laboratory method. DNA microarrays consist of numerous DNA probes, anchored at defined positions within a two-dimensional grid. These microarrays are used to screen for the presence or absence of a multitude of target polynucleotides in a single assay, and thus, DNA microarrays have utility for the collection of large amounts of experimental hybridization data in a short amount of time. The Applicants are incorrect in assuming that placement of an uncharacterized polynucleotide within a DNA microarray conveys the utility of the laboratory method to the individual piece of DNA. This asserted "utility" is not specific to the claimed polynucleotides, as any DNA can be placed into the microarray in order to carry out further research into the expression of said DNA. Even if expression of Applicants' claimed polynucleotide is altered by a test drug and is detected in a microarray for drug screening, the specification does not disclose any interpretation for the result. The Declaration fails to address the fact that information gained by the use of the claimed polynucleotides within a DNA microarray constitutes the experimentation needed in order to discover a patentable "real-world" utility for the claimed polynucleotides.. Further, the statement that one of skill in the art would have "specifically requested" the polynucleotide of SEQ ID NO:74 to be contained within an array" is not persuasive. The presence of the claimed polynucleotide in a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at. 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. °101.

In the middle of page 14 of the response, Applicant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Applicant points to Dr. Bedilion's pages of text and numerous sub-parts explaining the importance of this technology. Applicant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the importance of toxicity testing. This is not found to be persuasive. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

In the second paragraph of page 15 of the response, Applicant argues that the examiner does not address the fact that, as described on pages. 14, 56, 58-59 and 67-68 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Applicant concludes that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it and this can be said for any polynucleotide. Thus, this asserted utility is not specific.

At page 15, third paragraph of the response, Applicant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Applicant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

On page 16 of the response, applicant refers to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522). Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. This is not found to be persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph.

Applicant refers to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology testing at pp. 16-17 of the response. Applicant specifically sites Rockett et al (Xenobiotica, 1999, vol. 29, pp. 655-691) who state that new pharmacological agents can be screened by microarrays comprising genes whose function are unknown. Rockett et al teach that new drugs can be compared to drugs with known function and efficacy using said microarrays, and new drugs yielding expression patterns that are similar to know drugs can then be selected for further testing (abstract, lines 4-7, and page 656, lines 23-35). Thus, Rockett et al teach that a microarray need not comprise genes having known function. However, this does not impart a patentable utility to the instant polynucleotide, as any orphan gene can be used in the microarrays described by Rockett et al.. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is a not substantial.

Beginning at p. 17 of the response, Applicant argues that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease, and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Applicant argues that toxicology testing is a well-established utility and concludes that the claimed

polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at the bottom of page 18 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put. With regard to drug discovery and development, Applicant asserts expression profiling as one use of the claimed polynucleotide. Applicant refers to recent developments, on page 19 of the response as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Applicant is incorrect in assuming that discoveries made using other genes, versus the instant polynucleotides, influence the patentability of the claimed polynucleotides.

Applicants argue on page 20 of the response, that commercial success derived from the sale of polynucleotides databases comprising expressed genes lends credence to the assertion that the instant polynucleotides add "more than incremental benefit to the drug discovery and development process" Applicant argues that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest in the instant appeal. Applicant urges that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Applicant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. ° 101 for lack of operability can be overcome by a showing of actual use or commercial success. The instant issue is not lack of operability but whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.. Furthermore, although the sale of a newly identified cDNA to other researchers who would then attempt to elaborate a functional use for any potential encoded protein may be lucrative, it is the responsibility of the applicants, not the purchaser, who must disclose the specific use of the protein in order to satisfy the requirements of patent law. For these reasons, utility cannot be equated to commercial success.

Applicant argues on page 20 that the examiners rejections are without merit as a matter of law and of fact. The essential disagreement seems to be that the asserted utilities for the claimed polynucleotides are not specific, substantial and credible.

Applicant argues on page 20, that the precise biological significance or function of an expressed polynucleotide is not required to demonstrate utility. The examiner agrees that in cases where an empirical association between a polypeptide or polynucleotide and a disease state is set forth, it would not be necessary to demonstrate a precise biological role for the protein. Also in the event that the protein would have a well-established utility, such as a ligase, it would not be necessary to set forth an additional utility. However, for the reasons set forth above, the claimed polynucleotides or polypeptides encoded therefrom have neither specific correlation to a disease state or well-established utility. Applicant states on page 14, lines 4-7 that "It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States Patent". The examiner agrees with this analysis. However, as the specification is lacking any empirical correlation with a disease state or a well-established utility for the claimed polynucleotides or

polypeptide encoded thereby, the instant specification does not fulfill the requirement for a United States Patent. Furthermore, not all disclosures in technical journals necessarily fulfill the requirements of "real world" utility. Applicant cites the USPTO utility guidelines and quote "The utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has gene regulating activity". In the absence of a specific function for the encoded product, a empirical correlation with a disease state would be adequate to establish patentable utility. The specification has provided neither a specific association with a disease state nor a specific gene or receptor which is regulated by the encoded proteins.

At page. 22 of the response, Applicant argues that the utility of the claimed polynucleotide can be imputed based on "membership in a class of useful products". Applicant argues that as long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility. This has been considered but not found persuasive. In order to satisfy the utility requirement it is necessary for a specific, substantial and credible utility to be disclosed. Obtaining a U.S. patent is not based on a statistical probability of utility. Further, the specification has not asserted an art recognized class of compounds to which the disclosed polypeptides would belong. Instead applicants argue that the disclosed polypeptides belong to the class of "expressed polynucleotides" which has been pre-selected by nature to be useful (bottom of page 22), this has been considered but not found to be persuasive. In order to obtain a U.S. patent, it is applicant's responsibility to determine the specific, substantial and credible use that was pre-selected by nature. Applicant further argues that the demonstration that the claimed polynucleotide encodes a polypeptide that is expressed by humans is more than sufficient to make it useful for the diagnosis and treatment of diseases associated with cell proliferation, particularly immune responses and cancers. Applicant states that NHRP-1 has been shown to be expressed in cDNA libraries associated with cancer or inflammation and that the examiner must accept these facts or provide sound scientific reasoning to the contrary. This has been considered but not found persuasive. The examiner has not challenged the fact that the claimed polynucleotides can be found in libraries associated with cancer and inflammation. The examiner is challenging the lack of evidence that the claimed polynucleotides are indicative of a pathological state such as cancer or inflammation. actin and histone genes are expressed in diseased tissues, but as they are constitutively expressed in all tissues, they are not indicative of a specific pathological state.

Applicant agues on page 23 of the response, that because the uses of the claimed polynucleotides include toxicology testing, drug discovery and disease diagnosis which are practical uses beyond mere study of the polynucleotide itself, the claimed invention has substantial utility. For the reasons stated above, the instant specification has provided no disclosure on the use of the claimed polynucleotides in disease diagnosis. Using the claimed polynucleotides in a panel or array of polynucleotides to obtain a pattern of changes resulting from xenobiotics of unknown function, as proposed by Rockett et al, does not impart a specific, substantial and credible utility to the claimed polynucleotide as any orphan polynucleotide can be used for such purpose.. Applicant argues that the claimed polynucleotides would be useful in chromosomal mapping. However, as stated above, any expressed polynucleotide can be used to hybridize to a chromosome, and therefore this utility is not specific to the instant expressed polynucleotide. If, however, the claimed polynucleotides had been disclosed as mapping to a chromosomal location associated with a specific disease state such as a chromosomal breakpoint associated with leukemia, or a chromosomal locus which was amplified in specific cancers, and the specification asserted that the claimed polynucleotides could have been used as a chromosomal probe related to said cancers, such would have been accepted as a patentable utility even though it is unrelated to the function of the polypeptides encoded by the claimed polynucleotides.

Applicant agues on page 24 that differential expression associated with a disease state is irrelevant to toxicology testing. Applicant continues to allege that the claimed polynucleotides can be useful for toxicology testing in drug discovery without any knowledge of differential expression or disease association. Clearly any expressed polynucleotide can be used in the "open system" as set forth by Rockett et al as the first generation screen for patterns of gene changes based on exposure to a xenobiotic (Rockett et al page 656, lines 23-35). The technique describe by Rockett does not impart patentable utility to the claimed polynucleotides because it can be preformed with any polynucleotides. Therefore, it is not specific to the instant polynucleotides. On pages 24-26 applicant interpreted the utility guidelines. Applicants state that although the utility guidelines prohibit a "throwaway" utility, they do not preclude a "general" utility. Applicant admits that this is contrary to what has been set forth in the training materials which expressly require a specific and substantial utility. Applicant concludes that the training

materials are inconsistent with the law. This issue will not be addressed because an Examiner has no authority or specific knowledge to comment on the legality of the Guidelines.

Applicant argues on page 26 that the rejection under 35 U.S.C. 112, first for lacking utility must be reversed, as the utility rejection is improper. This is not persuasive as the utility rejection is maintained for reasons of record.

5. Applicant states in section III (A) (bottom of page 17 to the top of page 18) that the Examiner does not disprove the following: 1) that the claimed polynucleotide of SEQ ID NO:74 encoding the NHRP polypeptide having the amino acid sequence of SEQ ID NO:37 is expressed in humans; and 2) that all, or almost all, polynucleotides expressed in humans have specific and substantial utility for measuring undesired side effects of drug candidates in toxicological testing. However, part 2 of that statement was never agreed upon by the examiner. Specifically it was stated on page 17 of the previous Office action that

"Applicant further argues that the demonstration that the claimed polynucleotide encodes a polypeptide that is expressed in humans is more than sufficient to make it useful for the diagnosis and treatment of diseases associated with cell proliferation, particularly immune responses and cancers. Applicant states that NHRP-1 has been shown to be expressed in cDNA libraries associated with cancer or inflammation and the examiner must accept these facts or provide sound scientific evidence to the contrary. This has been considered but not found persuasive. The examiner has not challenged the fact that the claimed polynucleotides can be found in libraries associated with cancer and inflammation. The examiner is challenging the lack of evidence that the claimed polynucleotides are indicative of a pathological state such as cancer or inflammation. Actin and histone genes are expressed in diseased tissues, but as they are constitutively expressed in all tissues, they are not indicative of a specific pathological state."

Based on the above, it is clear that the examiner has not agreed that "all, or almost all, polynucleotides expressed in humans have specific and substantial utility".

Applicant argues that it follows that the claimed invention is by more than a reasonable probability useful. This argument is not relevant. In order to satisfy the utility requirement under 35 CFR 101, the specification must assert a specific, substantial and credible utility. for the reasons of record set forth in the previous Office action, the specification has failed to do so.

Applicant states that the examiner never assails or even addresses this compelling logic and continues to insists that applicant prove not only reasonable probability of utility but also the "biological role", "biological significance" or evidence of "differential expression" of the claimed polynucleotides or encoded polypeptides. The examiner agrees that this is so, because firstly, applicants arguments that any expressed human polynucleotide is useful and therefore fulfills the utility requirements, are faulty. By providing a biological role, biological significance or evidence of differential expression, there would be some means to evaluate the probability of utility. without such disclosure, applicant s invention is lacking specific and

substantial utility. thus, the examiner is not requiring applicant to prove not only reasonable probability of utility because disclosure of the biological role, biological significance disease association or evidence of differential expression would enable the examiner to discern the relative probability of utility. Applicant has stated on page 18, lines that the claimed polynucleotide is part of a narrow group consisting of the family of expressed polynucleotides and dismisses the necessity of providing "biological role" biological significance" disease association or "evidence of differential expression as "utterly irrelevant to the analysis. This is not persuasive. The utility requirement requires that the invention be specific and substantial. the family of "expressed polynucleotides" included every expressed polynucleotide. This cannot be considered by any means a narrow group, and the property of being expressed is shared by a universe of other polynucleotides, and therefore cannot be a specific utility nor a substantial utility because applicant has not divulged a real world use for the instant polynucleotide as indicated on page 6, lines 4-12 of the previous Office action.

In section III (B) of the response applicants maintain that the claimed uses of toxicology testing and gene expression monitoring assays meet the requirement that the claimed invention yield a "specific benefit". Applicant asserts that these uses constitute more than "further research" into the claimed invention itself. Part 1 states that "biological function, differential expression, or disease association is irrelevant to utility". Applicant contends that the examiner "continues to ignore" other utilities discussed in the specification or well known in the art". This has been considered and not found persuasive. The examiner has not ignored applicants allegation that the claimed polynucleotide could be used in toxicology test and gene expression monitoring assays as applicants arguments regarding such were responded to by the examiner on pages 9-15 of the previous Office action. Applicant states on page 19 of the response that applicant has demonstrated a utility for the claimed SEQ ID NO:74 polypeptide apart from the need for further experimentation and that utility exists today regardless of the biological function, disease association or differential expression of the claimed SEQ ID NO:37 or 74. This has been considered but not found persuasive, as no specific or substantial utility was stated in this paragraph and argument without evidence is unpersuasive. In the following paragraph, applicant states that the claimed polynucleotides or polypeptides encoded therefrom are useful for measuring the toxicity of drug candidates targeted to other polynucleotides or polypeptides

regardless of any possible utility for measuring properties of the claimed polynucleotides or encoded polypeptides. This has been considered but not found persuasive. If the expression of the claimed polynucleotide were casual or associatively linked to the expression of another polynucleotide that had a specific, substantial utility this would be the case, as the instant polynucleotide or the polypeptide encoded therefrom could be used as a surrogate to the "other" polynucleotide having the specific and substantial utility. However, that is not the fact pattern of the instant specification as no correlation with any other expressed polynucleotide has been set forth. Further, without a specific and substantial utility for the claimed polynucleotide, the inclusion of the claimed polynucleotide within an assay for measuring drug candidates specifically targeted to other polynucleotides cannot be of any utility for the assay because one of skill in the art would not know the significance of the impact of a drug candidate on the claimed polynucleotide, i.e. whether it was therapeutic or non-therapeutic if the expression of the claimed polynucleotide was altered in a positive of negative fashion, or whether the down regulation or upregulation of the claimed polynucleotide was indicative of a toxic effect. Thus, applicants arguments on this point are without merit.

In section 2 of part III (B) of the response, applicant criticizes the examiner for not accepting the Bedilion declaration as fact, and contends that "The examiners arguments amount to nothing more that the Examiner's disagreement with the Bedilion declaration and the Applicants assertions about the knowledge of a person of ordinary skill in he art and is tantamount to the substitution of the Examiners own judgment for that of the Applicants expert". This has been considered and not found persuasive. It is noted that the "Bedilion Declaration" does not present any concrete evidence for a specific and substantial utility for the claimed polynucleotides or the polypeptides encoded therefrom, and does not add any evidence to the instant disclosure regarding the specific and substantial utility of the claimed polynucleotide. Section 2164.05 of the MPEP states

> The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); cf. In re Alton, 76 F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

The Bedilion declaration does not set forth any experiments wherein the polynucleotide of the instant invention were used in a way that would demonstrate a specific and substantial utility,

either before or after the filing date and contains no factual information, and is therefore deemed a conclusory statement. The arguments presented in the declaration are essentially the same as the arguments presented in the response and no further information is gained from said Declaration. Applicant's statement that that "one of skill in the art reading the specification at the time the parent Lal '870 application was filed would have understood that specification to disclose the use of the claimed polynucleotides in gene expression monitoring for toxicology testing and drug development and the diagnosis of disease" is not persuasive. If the declaration had presented concrete evidence of specific and substantial utility for the disclosed polynucleotide that was enabled by the specification as filed, the Declaration would have been successful at overcoming the rejection under 35 U.S.C. 101. However, the Declaration provided no such information. Thus the disagreement with the declaration is summarized by "what one of skill in the art would have understood at the priority date". This is not found persuasive, because in order to overcome the utility requirement a specific and substantial utility has to be set forth in the specification. An arguments about one of skill in the art would have understood at the time of filing is not relevant to the issue at hand.

Applicant argues on page 20 of the response that the Bedilion Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target, and minimal effects on all other biological targets". Applicants argue that this means that if the expression of a particular polynucleotide is effected in any way by exposure of the test compound then the change in expression is an indication that the test compound may have undesirable toxic side effects and that it is important to note that such an indication of possible toxicity is specific not only for each compound tested but for each and every individual polynucleotide whose expression is being monitored. This has been considered but not found persuasive. There would be nothing specific to be gained by the use of the instant polynucleotide as a control versus any other polynucleotide, thus the utility would not be specific.

On page 21 of the response applicant states that the examiner continues to view utility in toxicology testing as requiring knowledge of the biological function or disease associated or differential expression of the claimed polynucleotides. Applicant again states that the claimed polynucleotide is useful for measuring the toxicity of drug candidates which are targeted not to

the claimed polynucleotides but to other polynucleotides, which is essentially the same arguments refuted in the above paragraph. To reiterate, the use of the claimed polynucleotide to measure the toxic effect of drug candidates on other polynucleotide which are the actual targets of the test does not constitute a specific utility as one of skill in the art could substitute any polynucleotide for the instant polynucleotide. Thus, the utility would not be specific. Applicants quote for the previous response stating "To meet the requirement of sections 101 and 112 of the Patent Act, the patent need only show that the claimed invention is "practically useful"...and confers a "specific benefit" to the public. The examiner contends that without a biological activity or demonstration of empirical correlation with a disease state, the claimed polynucleotides are not practically useful and do not confer a specific benefit to the public. It is the examiners position that upon reading of the specification, one of skill in the art would not be able to diagnose a disease state or treat a disease state in a human or other animal. The claimed polynucleotides would not be specifically or substantially useful in toxicology testing or drug development because nothing is disclosed about the expression of the claimed polynucleotide. therefore, one of skill in the at could not judge the effect of a substance against the expression of the claimed polynucleotide not knowing if the upregulation or downregulation of said polynucleotide is indicative of toxicity or a pathological state.

Applicant quotes the previous response instating practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite" not particular...Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. The examiner agrees with this statement. However, that is not the fact pattern in the instant invention. For example, a polynucleotide encoding a polypeptide that is a marker for breast cancer has a specific and substantial utility. It would not be "unique" in that there are other known polynucleotides which are markers for breast cancer, however, and such disclosure would satisfy the utility requirement because the use of the claimed polynucleotide would be both specific (correlated with breast cancer) and substantial (tumor marker) .

In section 3 of part III, B of the response, applicant argues that it is not necessary to disclosure the particulars of toxicology testing in the specification, as such uses are well established in the art. This is not a persuasive argument. Without a disclosure that the

expression of the claimed polynucleotide is a surrogate for the toxic effect of a drug in a particular tissue or organ, the utility is again nonspecific because any polynucleotide can potentially be used in toxicology testing if a correlation between the expression of the polynucleotide and the response of a cell or tissue to a toxic substance is set forth. The specification fails to provide this disclosure. Applicant continues to state that the examiner's position amounts to nothing more than the examiners disagreement with the Bedilion declaration and alleges that the examiner is substitution her judgment for that of the applicants expert and applicants assertions about the knowledge of a person of ordinary skill. Applicant contends that the examiner must accept Applicants assertions to be true. This again has already been answered above. The applicants expert has not provided any factual information regarding the use of the claimed polynucleotides, but instead provided the same arguments as presented in the response. Thus, the declaration did not add any information to the arguments of the response.

Applicant argues in section 4, on page 22 that the examiner stated that a utility shared by a large class is somehow not a utility. Applicant is again misconstruing the examiners position. On page 14, lines 8-16 of the previous Office action it was stated that for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at the bottom of page 18 of the response, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. As can be seen from the quote from the previous Office action, the examiner was pointing out why the use of the instant polynucleotide in toxicology testing was not a "well-established" utility. Thus, applicants comment that membership in a general class of products was "somehow not a utility" is misconstruing the examiner position. Applicant argues that nothing in the law says that an invention must have a "unique" utility. The examiner again agrees with this point, but it the same point that was argued above, that in the case of a shared utility such as a tumor marker,

each member of the group shares the same utility, but each marker, such as a marker for breast cancer, must have a specific utility. Membership in the class of tumor markers does not "destroy" a polynucleotides utility as alleged by applicant.

Applicant argues on the top of page 23 that although it is true that just about any expressed polynucleotide will have use as a toxicology control, the point is that the invention provide a useful measuring stick regardless of whether there is or is not differential expression and that makes the invention useful today for real-world purposes. Once again this is not persuasive, as the use of the claimed polynucleotide as a control would not add any information to a gene expression or toxicology assay regarding the response of the cell to the drug or toxic chemical as the specification does not disclose the biological significance of the expressed polynucleotide. therefore, the instant polynucleotide could be substituted with any other polynucleotide. Therefore, the utility is not specific.

Applicants argue in section 5 on page 23 that the examiner was wrong about the usefulness of the claimed polynucleotide in toxicology testing because the said polynucleotides would not be used as an object of the research. Applicant contends that the claimed polynucleotides are research tools used to assess the toxicity of drug candidates which are specifically targeted to other polynucleotides and that it would be the "other" polynucleotides which would be the target of the research. This has been considered but not found persuasive. A polynucleotide can only be used a s control polynucleotide when the conditions governing its expression would be known. Thus, actin can be used as a control in some experiments because it is would be expected that the expression of actin would not change during the confines of the experiment. such is not the case for the instant polynucleotide. No information regarding the conditions governing the expression of the instant polynucleotide has been set forth in the specification. Therefore its use as a control would be uninformative. It is conceivable that the expression of the claimed polynucleotide could increase or decrease in response to a drug or chemical, therefore, it would not be useful as a control polynucleotide without information regarding the response of the expression of the claimed polynucleotide to drugs or toxic chemicals. If the expression of the claimed polynucleotide were to be studied coupled with the expression of another target polynucleotide, then that would indeed constitute further research on

the claimed polynucleotide because further information regarding the expression of the claimed polynucleotide under the influence of drugs or toxic chemical would be ascertained.

On the bottom of page 23 applicant alleges that the examiner is ignoring the teaching of the Brown patent cited by Bedilion in his declaration. Applicant states that the Brown patent discloses "an array of cDNA clones representing genes " which is hybridized with total cDNA from an organism to monitor gene expression for research or diagnostic purposes...This two color experiment can be used to monitor gene expression in different tissues types, disease states , response to drugs or response to environmental factors". This has been considered but not found persuasive. To include the instant polynucleotide in such an array would constitute further research on said polynucleotide as it would potentially reveal: tissue specific expression, differential expression correlated to disease state, the expression of the claimed polynucleotide in response to drugs or environmental factors. The polynucleotide would not have any substantial use as a control in the above described microarray because its response to toxic drugs, chemical and environmental factors could not be predicted, therefore comparisons between the expression of target genes and the claimed polynucleotide could not be made using information form the claimed polynucleotide that contributed to the measurement of the target gene. To put the claimed polynucleotide in such arrays would be indisputably research on the claimed polynucleotide itself.

Applicant argues in section 6 on page 24 that the examiner implied that a utility is not specific if the process carried out in applying that utility to an object can also be carried out on a different object. Again applicant misinterprets the examiners statement. On page 18 , lines 5-9, it was stated that "Using the claimed polynucleotides in a panel or array of polynucleotides to obtain a pattern of changes resulting from xenobiotics of unknown function, as proposed by Rockett et al, does not impart a specific, substantial and credible utility to the claimed polynucleotide as any orphan polynucleotide can be used for such purpose." Applicant asserts that this statement is "incorrect" because the fact that one can apply a given process to a number of different objects does not mean that the process is not a specific utility when applied to a particular object. The examiner contends that applicant is incorrect in interpreting the utility requirement. The process of putting the claimed polynucleotide in an array and hybridizing said array with polynucleotides taken from cells having been exposed to particular drugs or chemicals

without a doubt constitutes further research on the claimed polynucleotide. The claimed polynucleotide could not be used as a control polynucleotide because some expectation about the expression of the control polynucleotide must be known before the experiment is carried out. One of skill in the art must know with a reasonable expectation of success that the expression of the claimed polynucleotide would be unaltered, increased or decreased by the drugs, toxic chemical or environmental conditions used. Without that information the use of the claimed polynucleotide in said array is use-testing for said polynucleotide. As stated in the previous Office action (page 8, lines 17-19) "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. °101..

Applicant argues in the middle of page 24 that any toxicology test using a given expressed polynucleotide as a control is a distinct and unique toxicology test because the results of the test are dependent upon the identity of the expressed polynucleotide and that the results of a toxicology test using a given expressed polynucleotide is not interchangeable with a toxicology test using a different expressed polynucleotide. Applicant states that the fact that the same series of steps can be used to carry out such toxicology test does not prevent such test from being a specific utility. This has been considered but not found persuasive. The instant specification does not enable the use of the instant polynucleotide as a control in a toxicology test. As stated above, there is no teachings in the specification regarding the expression of the claimed polynucleotide under conditions of exposure of drugs and chemicals, thus one of skill in the art could not rely on knowledge gleaned from the instant disclosure in order to use the instant polynucleotide as a "control" in a toxicology test. Further, arguments regarding the use of the given polynucleotides as a control which is distinct and unique are moot because there is no enablement for the use of the instant polynucleotide as a control in the specification as filed. The specification does not teach that the instant polynucleotides are housekeeping genes or tissue specific genes, and therefore invariant in their expression. The instant specification does not assert that the expression of the instant polynucleotide increased or decreased after drug or toxin exposure. The specification does not teach that expression of the instant polynucleotide is indicative of cell growth or cell death. One of skill in the art would not use the claimed

polynucleotide as a control because there is no expectation of constancy, or positive or negative response to a specific physical or chemical agent. Regarding the distinctness and uniqueness of a toxicology test which included the instant polynucleotide, it is noted that said distinctness and uniqueness is only potential with regard to said polynucleotide as the no disclosure regarding the specific biological significance of said polynucleotide has been made. The fact that the same series of steps can be used to carry out such toxicology test is not relevant. What is relevant is the impact of the claimed polynucleotide on the interpretation of the experimental result. Because the biological function or significance or empirical correlation with a pathological state is not set forth for the instant polynucleotide or polypeptide encoded therefrom, no substantial conclusion can be drawn from said experiment because the inclusion of the claimed polynucleotide will not add any information to the assay. The only data that will be rendered from said experiment is relative between the "other" polynucleotide and the claimed polynucleotide. Because there would be no expectation of how the claimed polynucleotide would behave under circumstances of the assay, the experiment would only give information as to how the claimed polynucleotide did indeed act under the experimental conditions and thus would be only further experimentation on the claimed polynucleotide itself.

On page 25 applicant argues that in the case of a microarray, each individual polynucleotide included in such an array would have utility, because with the addition of each expressed polynucleotide to the pool of genes available for use in gene expression technology the more useful the microarray is for gene expression technology. It is noted that this statement is not substantiated with any reasoning which would point out why the instant polynucleotide would be selected for such an array, or what information could the instant polynucleotide provide to such an array except for further research on the properties of the polynucleotide itself. Applicant again states that the examiner is ignoring the teachings in the Bedilion declaration which is tantamount to substituting the Examiner's own opinion for that of the applicants expert. This has again been considered but not found persuasive. As pointed out above, the Bedilion Declaration does not include any teachings regarding the claimed polynucleotide. The declaration just re-iterates the arguments in the response and asserts that the claimed polynucleotide would be useful in microarrays for drug screening and toxicology testing. The Declaration provides no further information as to any specific, or substantial property of the

polynucleotide which would fulfill the utility requirement of 35 U.S.C. 101. Applicant notes that the Bedilion Declaration states "the specification of the Lal '870 application would have led a person skilled in the art on June 6, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of immune response and cancer to conclude that a cDNA microarray that contained the SEQ ID NO:74 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purpose contain the SEQ ID NO:74 polynucleotide" and "cDNAs containing microarrays containing the SEQ ID NO:74 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the SEQ ID NO:74 polynucleotide". These statements are again considered and again not found persuasive. It is noted that the Bedilion Declaration does not explain why a person of skill in the art would select the instant polynucleotide over any other polynucleotide for part of an array in screening new drugs for treatment of immune response and cancers. It can only be concluded that one of skill in the art would selected it for inclusion in the array to determine the expression pattern of the claimed polynucleotide and how or if said expression pattern was altered in response to drugs which affected cancers or the immune response and this is equivalent to further experimentation of the polynucleotide itself.

Applicant argues in section 8 on the bottom of page 8 that there are at least two patents claiming orphan receptors. This comment is noted, however, said patents are not under examination at this time.

Applicant states in section 9 on page 26 that toxicology testing using microarrays reduces time needed for drug development by weeding out compounds which are not specific to the drug target. It is deduced from this statement that applicant proposes that the instant polynucleotide can be used in a microarray to screen for compounds which are specific for the expression of a single target "other" polynucleotide and that if a given drug or compound influenced only the target polynucleotide, then the test would be a successful for the identification of a specific agent. This has been considered but not found persuasive for the reasons stated above. specifically that any other polynucleotide could be substituted for the instant polynucleotide in such an assay. Therefore the utility is not specific.

Applicant states in section 10 that "The Examiner's reliance on Brenner versus Manson is misplaced". Applicant argues that it is a given that the claimed invention disclosed in the Lal

'870 application is a useful tool in a number of gene expression monitoring application, therefore the precise biological function, disease association or differential expression is superfluous information. For the reasons set forth above, the examiner contends that the claimed polynucleotides are not a useful tool in gene expression studies because they add no information to the study, and without some knowledge of the biological, function, signification, differential expression or association with a pathological state the contribution to eh assay would not be substantial. Therefore, the need for this information is not superfluous in the establishment of utility. Applicant adds that the "uncontested fact" that the claimed invention already has a disclosed use as a tool and that available technology distinguishes it from those few claimed inventions found not to have utility. Applicant does not provide any reasoning, why after reading the Office action of Paper No. 12 one of skill in the art would have concluded said "uncontested fact" as every point made by applicant was deemed unpersuasive by the examiner. Applicant argues that the examiners unsupported statement that the case of Brenner versus Manson is analogous to the instant case is plainly incorrect. The examiner did not discuss Brenner versus Manson, but quoted only the conclusion stated by the court which can be applied to any invention. The examiner refers applicant to page 6, lines 2-3 of the previous Office action which state . "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. This is not a misplaced analogy, because clearly, inclusion of the claimed polynucleotide in an gene monitoring study would constitute only further experimentation into the expression of the polynucleotide itself. Applicant argues on page 27 that the steroid was not disclosed in the application and that, in contrast, the claimed polynucleotide is disclosed to be useful and it's utility was not then a matter of guesswork. Applicant goes on to reason that the instant invention is therefore not a DNA or protein sequence that might or might not be useful as a scientific tool. The examiner would like to point out that by applicant own reasoning any polynucleotide could be put into the microarray to screen drugs for specificity, and therefore neither specific nor substantial utility can b attributed to the instant polynucleotides. Applicant ends the argument by stating that the utilities disclosed in the application are for purposes other than the study of the claimed invention itself. However, this has been refuted by the examiner for the reasons set forth above, and thus the conclusion by applicant that "persons of skill in the art on reading of the Lal

'870 application would have believed that claimed polynucleotide to be so useful that they would request them to be included as probes in cDNA microassay for conditional gene expression analysis in association with identifying drugs for treating immune response and cancers is erroneous. As stated above, the inclusion of the claimed polynucleotide in gene monitoring studies would not add any information to the microarray because nothing is known about the biological significance, biological function, association with a pathological state or differential expression of the claimed polynucleotide, and thus inclusion of the claimed polynucleotide into said microarray would only be carried out for purpose of obtaining information of the expression of the claimed polynucleotides. The claimed polynucleotide would not have a specific use as a control polynucleotide in such a screening experiment because without some information regarding the biological significance, biological function, association with a pathological state or differential expression of the claimed polynucleotide no substantial conclusion would be drawn regarding the effect of a drug or environmental factor on a "target" polynucleotide as no expectation about the expression claimed polynucleotide could be used in the interpretation of the results. Applicants argue in the middle of page 28 that the claimed invention is more than "substantially likely" to be useful in a way that is utterly independent of knowledge of precise biological function as the Bedilion declaration and other evidence presented by Applicants demonstrates. This is unpersuasive. Neither applicant nor the Bedilion declaration has presented any evidence of a specific, substantial and credible utility for the claimed polynucleotide. Applicant states that the instant invention confers "real world" benefits to the public by enabling faster, cheaper and safer drug discovery processes and that the examiner is obliged by law to recognize this reality. This is not persuasive. Applicant is required to satisfy the requirement for a specific, substantial and credible utility under 35 USC 101. Neither the specification nor the Bedilion declaration has provided a specific, substantial and credible utility by means of evidence that the claimed polynucleotide fulfills the standard for a real world use for the reasons set forth in the Office actions of Papers No. 9 and 12. The essential disagreement is that applicant has provided a novel human expressed polynucleotide and applicant deems that this disclosure fulfills the requirements of 35 USC 101. The applicant has provided only the information that the polynucleotide is a human expressed polynucleotide and the DNA sequence of said polynucleotide. However, this disclosure of itself does not fulfill the requirement of the

Revised Utility Interim Guidelines issued by the PTO in 1999, which require a specific and substantial utility. By the analysis presented in the office actions of the Paper No. 9, 12 and the instant Office action, the examiner has held that no uses were disclosed for the instant polynucleotide which were both specific and substantial. The rejection is therefore maintained

6. In the event that applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to polynucleotides that encode SEQ ID NO:37; polynucleotides comprising SEQ ID NO:74, the complete complement of SEQ ID NO:74, an isolated polynucleotide consisting of a fragment of the complement of SEQ ID NO:74,; and an array comprising a polynucleotide complementary to SEQ ID NO:74, wherein said polynucleotide is completely complementary to SEQ ID NO:74; because the specification does not reasonably provide enablement for polynucleotides that encode a fragment of SEQ ID NO:37, polynucleotides encoding polypeptides having at least 95% identity to SEQ ID NO:37, polynucleotides comprising naturally occurring polynucleotides having at least 95% sequence identity to SEQ ID NO:74, an isolated polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:74, polynucleotides at least 95% identical to SEQ ID NO:74; microarrays or arrays comprising SEQ ID NO:74 or microarrays or arrays comprising polynucleotides at least 95% identical to SEQ ID NO:74. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A) As drawn to polynucleotides encoding a polypeptide comprising an amino acid sequence at least 95% identical to SEQ ID NO:37 and polynucleotides comprising a polynucleotide sequence at least 95% identical to SEQ ID NO:74

Claims 25, 28-30, 32, 33, 39, 41 and 43-45 encompass polynucleotides comprising non-disclosed nucleic acid sequences, that is polynucleotide variants of SEQ ID NO:74, polynucleotides which encode variant polypeptide of SEQ ID NO:37, and polynucleotides having 95% sequence identity to SEQ ID NO:74. The specification does not teach polynucleotides encoding a naturally occurring polypeptide having 95% identity to SEQ ID NO:37 or naturally occurring polynucleotides having 95% identity to SEQ ID NO:74. The specification states that alleles result from at least one mutation in the nucleic acid sequence and may result in mRNAs or polypeptides whose structure or function may or may not be defined (page 10, lines 1-4). The specification states that altered nucleic acid sequences encoding NHRP include those with deletions, substitutions or insertions of different nucleotides that result in a polynucleotide that encodes the same functionally equivalent NHRP (page 10, lines 8-10). However, the specification also states that variants of NHRP include amino acid sequences having non-conservative changes in the amino acid sequence (page 17, lines 11-12).

The claims are broadly drawn to variant polynucleotides and polynucleotides encoding variant polypeptides. The specification neither limits nor defines naturally occurring polynucleotide having 95% identity to SEQ ID NO:74 or naturally occurring amino acid sequences having 95% identity to SEQ ID NO:37. The specification neither limits nor defines fragments of the amino acid sequence of SEQ ID NO:37 for the reasons set forth in the rejection under 112, second paragraph, below. Further, the variants as defined in the specification include but are not limited to allelic sequences, altered NHRP and variants of NHRP. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a large species of polynucleotides that encode numerous proteins having neither structural nor functional identity with polynucleotides encoding SEQ ID NO:37 and no guidance has been given as to how to use these species. The specification has not shown that polynucleotides encoding polypeptides comprising variants of SEQ ID NO:37 or polynucleotide variants of SEQ ID NO:74 are capable of functioning as polynucleotides encoding SEQ ID NO:37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use the polynucleotides that encode the broadly claimed polypeptides. The relationship between amino acid sequence and protein function is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (Journal of Cell Biology, 1990, Vol. 111, pp.2129-2138) replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (page 2132 column 1 to page 2133 column 2). In the case of TGF alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect

biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the altered TGF alpha. (Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252, page 1250 bridging paragraph). These references demonstrate that even a single amino acid substitution or what appears to be a minor modification will often dramatically affect the biological activity of a protein. Clearly, it could not be predicted that a variant polynucleotide, or polynucleotide encoding a variant protein would have equivalent functional characteristic of the polynucleotide which encodes SEQ ID NO:37. Further, one of skill in the art would not be able to screen variant polypeptides based on functional characteristic because the specification has not disclosed any regulatory, structural of biochemical characteristic of SEQ ID NO:37. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variant polynucleotides, or polynucleotides encoding variant proteins.

Claim 33 is drawn to an isolated polypeptide which comprises 60 contiguous nucleotides of SEQ ID NO:74, the complementary sequences thereof, or a naturally occurring polynucleotide having 95% sequence identity to SEQ ID NO:74 or the complementary sequences thereof. It is noted that claim 33 encompasses both sense and anti-sense strands of SEQ ID NO:74 and the naturally occurring variant of SEQ ID NO:74, however the specification does not teach how to use a probe comprising a sense strand of SEQ ID NO:74 or a sense strand of a naturally occurring variant of SEQ ID NO:74. Aforesaid probes would hybridize to genomic DNA, and there are no teachings in the specification or any art of record to support the notion that binding of a probe to genomic DNA would be diagnostic for the diseases and conditions recited on page 56, lines 2-15, as the recited disorders are asserted to be associated with aberrant NHRP expression in contrast to the presence of the gene in the genome. Thus, it can be concluded that the specification does not teach a use for a polynucleotide probe comprising at least 60 contiguous nucleotide residues of SEQ ID NO:74, or a naturally occurring variant of SEQ ID NO:74. Furthermore, claim 33 is drawn to isolated polypeptides which comprise, rather than consist of, 60 contiguous nucleotides of SEQ ID NO:74 or a variant of SEQ ID NO:74, or the complements of either of the aforesaid polynucleotides. Given the broadest reasonable interpretation, the claim reads on a large genus of polynucleotides in excess of 60 nucleotides and the specification has not a use for the broadly claimed polynucleotides. The specification has not taught that a polynucleotide sequence comprising 60 contiguous nucleotides of SEQ ID NO:74 in addition to non-disclosed nucleotides would serve as a diagnostic indicator for the same disease states as SEQ ID NO:74. The specification has not taught that transferring 60 contiguous nucleotide of SEQ ID NO:74 into a longer polynucleotide sequence would result in polynucleotide encoding a polypeptide having the same functional characteristic of SEQ ID NO:37. It is well known in the art that proteins are folded three-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry (text), 1996, pp. 165-171). In any given protein amino acids distant from one another in the primary sequence may be closely located in the folded three-dimensional structure. (Mathews and Van Holde, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the NHRP of SEQ ID NO:37 protein can potentially radically alter the three dimensional structural environment in which the given fragment is located (Matthews in Perspectives in Biochemistry, 1989, Ed. H. Neurath, pp. 6-9, page 6, second column, first paragraph) and the consequences of the altered sequence environment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects must be considered with respect to protein function in addition to molecular aspects (Bork, Genome Research, 2000, vol. 10, pp. 398-400, p. 398, column 2, first paragraph). Furthermore, it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims would not share functional properties with the polynucleotides of SEQ ID NO:74 or encode proteins that share functional properties of SEQ ID NO:37. The function of the claimed polynucleotides cannot be predicted, and has not been taught by the specification. Thus, with the exception of a polynucleotide sequence consisting of 60 contiguous amino acid sequence of the complete complement of SEQ ID NO:74, one of skill in the art would be forced into undue experimentation in order to use the broadly claimed polynucleotides..

(B) An array comprising: SEQ ID NO:74, an array comprising a polynucleotide having at least 95% sequence identity to SEQ ID NO:74, an array comprising the complete complement of a polynucleotide having at least 95% sequence identity to SEQ ID NO:74

Claims 39 and 41 are drawn to arrays comprising fragments of the polynucleotides of claim 32 and 33. It is noted that the polynucleotides encompass both sense and anti-sense strands of SEQ ID NO:74 and variants of SEQ ID NO:74, and for the reasons states above, the specification is not enabling for probes consisting of the sense strand

of SEQ ID NO:74 or a variant of SEQ ID NO:74 as the probe would hybridize to genomic DNA. Further, the specification is not enabling for probes comprising fragments of the anti-sense strand of the variant of SEQ ID NO:74 as the specification has not taught how to use all the possible variants of SEQ ID NO:74 as stated in the rejection above, regarding naturally occurring polynucleotides having at least 95% sequence identity to SEQ ID NO:74. For these reasons, one of skill in the art would not know how to use the broadly claimed arrays for the detection of the diseases stated on page 56, lines 2-15.

(C) As drawn to polynucleotides encoding fragments of SEQ ID NO:37

Claim 25 is drawn in part to polynucleotides encoding immunogenic fragments of SEQ ID NO:37.. Claim 25 is also drawn in part to immunologically active fragments of SEQ ID NO:37.. The specification states that antibodies which specifically bind NHRP may be used for the diagnosis and conditions or diseases characterized by expression of NHRP, or in assays to monitor patients being treated with NHRP, agonists, antagonists or inhibitors (page 54, lines 17-19). Further, the specification has not provided teachings for how to use any antibody generated to peptides of SEQ ID NO:37. The specification contemplates the administration of antibodies which specifically bind NHRP may be used directly as an antagonist or may be used indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express NHRP. The specification has not taught how to make antibodies which antagonize the action of the NHRP of SEQ ID NO:37 as the specification has not taught a receptor or a ligand for NHRP. The specification has not taught if NHRP is expressed on the cell surface as an antigenic target, or if NHRP is involved in signal transduction within the cytosol, or if NHRP binds directly or indirectly to nuclear DNA. Without a specific function attributable to the NHRP of SEQ ID NO:37 one would not know if an antibody which bound to SEQ ID NO:37 was able to antagonize said function or inhibit a putative binding with a ligand or receptor. Further, with regard to the delivery of a pharmaceutical to a disease site, the specification does not teach that SEQ ID NO:37 is accessible on the cell surface. Given this lack of teaching, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the broadly claimed fragments of SEQ ID NO:37.

The specification provides insufficient guidance with regard to all of the issues above and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention. Applicant argues on pages 27-29 that the specification discloses how to make and use the claimed variants, fragments and mRNA equivalents. This has been considered but not found persuasive. The cited portions if the specification describe only general methods of manipulating recombinant polynucleotides and chemically synthesizing fragments of the claimed polynucleotides. Because the specification has not provided a specific use or function for the claimed polynucleotides, the claimed variants, fragments and mRNA equivalents cannot be limited by a specific use or function and potential include polynucleotides having alternative uses or functions, beyond those yet not be established for SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37 which are not set forth in the specification. Applicant argues on the top of page 29 that it would not be undue experimentation to use a polynucleotide encoding an immunogenic fragment of SEQ ID NO:37 because only antibody binding need be tested. This has been considered but not found persuasive. The generation of an antibody or an immunogen-antibody complex cannot be regarded as enablement for "how to use" the immunogenic fragment. Because the specification has not defined a specific disease or condition related to the instant polynucleotides, one of skill in the art would not know how to use antibody resulting from the immunogenic fragment for detection or diagnosis of a disease. One of skill in the art would not know how to use a the instant polynucleotides encoding the immunogenic fragment for a preparation of a vaccine against a specific disease or condition as said disease or condition has not been identified. Applicant argues that the references of burgess et al, Lazar et al, Mathews and Van Holde, Mathews and Bork do not support the examiners position that the claimed variant structures may have different biological functions than SEQ ID NO:74 and 37. Applicant again argues that all of the variants and fragments claimed are enabled by virtue of the fact that they are expressed polynucleotides, and additionally able to be used in toxicology testing. Applicant states that the examiner has confused use with biological function. This has been considered but not found persuasive. For the reasons states above, a expressed polynucleotide does not have a specific utility by virtue of its being an expressed polynucleotide or being included in a microarray. The examiner has not confused use with function, however, the disclosure enables neither use not function for the disclosed polynucleotide of SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37.

7. Applicant argues that it is improper to reject the instant invention under 112, first paragraph, because the rejection under 35 USL 101 is faulty. This is not persuasive. To obtain a valid patent, a patent application must be filed that contains a full and clear disclosure of the invention in the manner prescribed by 35 U.S.C. 112, first paragraph. The requirement for an adequate disclosure ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent. Because the disclosure is lacking a specific and substantial utility for the reasons set forth in Paper No. 9, 12 and above, the invention fails to insure that the public receives beneficial information for how to make and use the claimed polynucleotide. Further, the claims are broadly drawn to variant polynucleotides and polynucleotides encoding variant polypeptides. The specification neither limits nor defines naturally occurring polynucleotide having 95% identity to SEQ ID NO:74 or naturally occurring amino acid sequences having 95% identity to SEQ ID NO:37. The specification neither limits nor defines fragments of the amino acid sequence of SEQ ID NO:37 for the reasons set forth in the rejection under 112, second paragraph, below. Further, the variants as defined in the specification include but are not limited to allelic sequences, altered NHRP and variants of NHRP. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a large species of polynucleotides that encode numerous proteins having neither structural nor functional identity with polynucleotides encoding SEQ ID NO:37 and no guidance has been given as to how to use these species. The specification has not shown that polynucleotides encoding polypeptides comprising variants of SEQ ID NO:37 or polynucleotide variants of SEQ ID NO:74 are capable of functioning as polynucleotides encoding SEQ ID NO:37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use the polynucleotides that encode the broadly claimed polypeptides. The relationship between amino acid sequence and protein function is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (Journal of Cell Biology, 1990, Vol. 111, pp.2129-2138) replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (page 2132 column 1 to page 2133 column 2). In the case

of TGF alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the altered TGF alpha. (Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252, page 1250 bridging paragraph). These references demonstrate that even a single amino acid substitution or what appears to be a minor modification will often dramatically affect the biological activity of a protein. Clearly, it could not be predicted that a variant polynucleotide, or polynucleotide encoding a variant protein would have equivalent functional characteristic of the polynucleotide which encodes SEQ ID NO:37. Further, one of skill in the art would not be able to screen variant polypeptides based on functional characteristic because the specification has not disclosed any regulatory, structural of biochemical characteristic of SEQ ID NO:37. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variant polynucleotides, or polynucleotides encoding variant proteins.

Applicant argues on the bottom of page 29 that the specification enables the isolation of naturally occurring polynucleotide variants by teaching how to find said variants. This has been considered but not found persuasive, The essential requirement to satisfy 112, first paragraph for enablement is how to make the disclosed invention. A disclosure of "how to find" is not a disclosure of how to make. Applicant further argues on the top of page 30 that the determination of the percentage identity is well known in the art. This has been considered but not found persuasive. Anyone can determine the percentage identity, however, there are no teachings in the specification how to use said variants having the claimed percentage identity. Applicant asserts that the variant polynucleotides would have the same utility as the instant polynucleotide of SEQ ID NO:74 by virtue of their being an expressed polynucleotide. This is not persuasive, for the reasons of record stated above, that one of skill in the art would not know how to use the claimed polynucleotide without further experimentation.

Applicant argues on page 30 that the specification is fully enabling for how to make the immunogenic fragment and cites page 47, lines 4-10 in support of this allegation. This has been considered but not found persuasive. It is set forth in 35 CFR 112, first paragraph, that enablement for both making and using of the invention is required. Applicants cited text refers to the use of the immunogenic fragment to make antibodies which bind to the polypeptide

encoded by the claimed polynucleotide. Applicant has not taught how o use an antibody that binds to the polypeptide encoded by the claimed polynucleotide because there is not biological function, significance, or correlation to a disease state associated with the disclosed polynucleotide. One of skill in the art would not know how to use antibodies which bind to SEQ ID NO:37 or antibodies which bind to variant of SEQ ID NO:37 having at least 95 % sequence similarity to SEQ ID NO:37 for the same reason. The specification contemplates the administration of antibodies which specifically bind NHRP may be used directly as an antagonist or may be used indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express NHRP. The specification has not taught how to make antibodies which antagonize the action of the NHRP of SEQ ID NO:37 as the specification has not taught a receptor or a ligand for NHRP. The specification has not taught if NHRP is expressed on the cell surface as an antigenic target, or if NHRP is involved in signal transduction within the cytosol, or if NHRP binds directly or indirectly to nuclear DNA. Without a specific function attributable to the NHRP of SEQ ID NO:37 one would not know if an antibody which bound to SEQ ID NO:37 was able to antagonize said function or inhibit a putative binding with a ligand or receptor. Further, with regard to the delivery of a pharmaceutical to a disease site, the specification does not teach that SEQ ID NO:37 is accessible on the cell surface. Given this lack of teaching, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the broadly claimed fragments of SEQ ID NO:37.

Applicant argues on the bottom of page 30 that the claimed polynucleotide variants, fragments, RNA equivalents and complementary sequences are useful for the same purpose as the polynucleotide sequence of SEQ ID NO:74. This has been considered but not found persuasive, because the claims are not limited to polynucleotides having functional attributes which are the same as that of SEQ ID NO:74. When given the broadest reasonable interpretation, such a limitation cannot be imposed in the evaluation of the scope of the claim. Applicant is again relying on the argument that any polynucleotide can be used in toxicology testing by virtue of being an expressed polynucleotide for the reasons that were refuted in the response to the rejection under 35 USC 101 above. Applicant again states that the examiner has confused use with function. In the instant case, the "use" of the claimed polynucleotide cannot be separated from its function. Without knowing the biological significance, function,

differential expression or association with a pathological state, one of skill in the art would be forced to do additional experimentation in order to determine the function of the claimed polynucleotide or protein encoded therefore in order to use the claimed polynucleotide as inclusion of the claimed polynucleotide in gene monitoring studies as a control would lead to erroneous results. Applicant further argues at the top of page 31 that the specification discloses the use of complementary polynucleotides in antisense technology, and the use of the claimed polynucleotide in arrays and therefore has fully satisfied the 'how to use" requirement of 112, first paragraph. This has been considered but not found persuasive. Claim 33 is drawn to an isolated polypeptide which comprises 60 contiguous nucleotides of SEQ ID NO:74, the complementary sequences thereof, or a naturally occurring polynucleotide having 95% sequence identity to SEQ ID NO:74 or the complementary sequences thereof. It is noted that claim 33 encompasses both sense and anti-sense strands of SEQ ID NO:74 and the naturally occurring variant of SEQ ID NO:74, however the specification does not teach how to use a probe comprising a sense strand of SEQ ID NO:74 or a sense strand of a naturally occurring variant of SEQ ID NO:74. Aforesaid probes would hybridize to genomic DNA, and there are no teachings in the specification or any art of record to support the notion that binding of a probe to genomic DNA would be diagnostic for the diseases and conditions recited on page 56, lines 2-15, as the recited disorders are asserted to be associated with aberrant NHRP expression in contrast to the presence of the gene in the genome. Thus, it can be concluded that the specification does not teach a use for a polynucleotide probe comprising at least 60 contiguous nucleotide residues of SEQ ID NO:74, or a naturally occurring variant of SEQ ID NO:74. Applicant argues on the bottom of page 31 that the examiner has confused use with biological function, and continues to allege that one of skill in the art can use variants and fragments of SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37 without knowing the biological function, significant, correlation with a pathological state or differential expression of said polynucleotides. This is not found persuasive for the reasons set forth in the rejection under 35 USC 101, above regarding the polynucleotide of SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37.

Applicant argues on the bottom of page 31 that a probe comprising a fragment of the sense strand of SEQ ID NO:74 or a naturally occurring variant of SEQ ID NO:74 is enabled by the instant specification and cites the instant specification on page 57, lines 23-30 which describe

oligomer nucleotide primers for pcr amplification. This has been considered but not found persuasive. The claims under rejection for comprising the "sense" strand are claims 39 and 41 drawn to arrays comprising an isolated polynucleotide comprising 20 contiguous nucleotides of the polynucleotide of claim 32 which encompasses the sense strand. These oligonucleotides affixed in a distinct physical location on a solid substrate can not be substituted for the oligonucleotide primers of a PCR reaction which include DNA polymerase, and nucleotides. These arrays are clearly used for hybridization reactions not PCR amplification. Applicants argument is unconvincing.

8. The rejection of claims 25, 28, 29, 30, 32, 33, 39, and 41 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. The rejection of claims 44 and 45 is made for the same reasons.

Applicant has amended the claims to recite a 95% sequence identity in place of a 90% sequence identity. However, the rejection was made on the basis of the limitation of "naturally occurring" which was not contemplated by the specification or claims as originally filed as a limitation for the claimed variants. It is noted that claim 33 persists in incorporating the limitation of 60 consecutive nucleotides of claim 32, although page 17, lines 14-17 state that the new limitation of "60 consecutive nucleotides" was not contemplated in the specification or claims as originally filed. The specification contemplates allelic sequences on page 10, lines 1-7, and NHRP variants having 90% sequence identity the NHRP sequence, however, this is not adequate basis for naturally occurring amino acid sequences having at least 90% identity to SEQ ID NO:37 or naturally occurring polynucleotide sequences having 90% sequence identity to SEQ ID NO:74, or a variant which is at least 95% identical to SEQ ID NO:37 encoded by SEQ ID NO:74, or a polynucleotide comprising an allelic sequence having at least 95% identity to SEQ ID NO:74 The specification or originally filed claims did not contemplate arrays comprising oligonucleotides complementary to polynucleotide having 95% identity to SEQ ID NO:74.

Because of the introduction of new matter, one of skill in the art would not be reasonably assured that applicant had possession of the claimed invention at the time of filing.

Newly added claim 44 is drawn to an isolated polynucleotide of claim 23 encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:37 encoded by an allele of SEQ ID NO:74. Claim 45 is drawn to a polynucleotide of claim 32 selected from the group consisting of an isolated polynucleotide of claim 32 comprising an allele of SEQ ID NO:74 at least 95% identical to SEQ ID NO:74 and a polynucleotide completely complementary to the aforesaid polynucleotide.

Applicant argues that the case law provides that applicant must convey with reasonable clarity to those skilled in the art that the invention is "whatever is now claimed". Applicant seems to deduce from this statement that the scope of the invention can be either narrowed or enlarged at will, as long as it is now claimed. However, this is not true. Applicant cannot introduce new matter into the disclosure or amend the claims by reciting specific embodiments which were not contemplated in the specification at the effective priority date. Such is the case here. Although applicant contemplated allelic variants in the specification as filed, the recitation of a naturally occurring variant with at least 95% sequence identity to SEQ ID NO: does not encompass the same scope as "an allelic variant" or a "variant", therefore, this is new matter. Applicant argues that the specification on page 33, lines 11-18 states "The invention contemplates each and every possible variation of nucleotide sequence that could be made by selecting combinations based on possible codon choices. These combination are made in accordance with the standard triplet code as applied to the nucleotide sequence of naturally occurring NHRP and all such variation are to be considered as being specifically disclosed." This has been considered but not found persuasive. The cited text is a contemplation of all polynucleotides encoding NHRP as a result of degenerative coding sequence. The cited text has no nexus to naturally occurring variants or allelic sequences. Further applicant argument on the bottom of page 33 stating that "while the originally filed application does not contain a verbatim recitation of the instant rejected claims it is apparent that the inventors contemplated naturally occurring polynucleotide sequences of NHRP molecules at least 95% identical to the polynucleotide sequence of SEQ ID NO:74 by virtue of contemplating naturally occurring polypeptide sequences of NHRP molecules at least 95% identical to SEQ ID NO::37. This has been considered but not found persuasive. Firstly the specification does not contain reference to "naturally occurring polypeptide sequences at least 95% identical to SEQ ID NO:37". It is noted that applicant did not offer a page and line number to indicate the support for that limitation, and furthermore, new claims drawn to allelic sequence at least 95% identical to SEQ ID NO:74 are also not supported by the specification, as the qualifier of 95% sequence identity was not set forth in the context of said allelic variant.

Applicant further argues in the middle of page 34 that the specification as filed supported arrays comprising olgionucleotides having 95% identity to SEQ ID NO:74 quoting the

specification at page 58, lines 8-9 which states " oligonucleotides derived from any of the polynucleotide sequences described herein may be used in microarrays". However, this argument is moot, as the claims drawn to microarrays were rejected on the basis of the dependence upon claim 32 drawn to naturally occurring variants having at least 95% identity to SEQ ID NO:74.

Applicant argues in part 2, on page 35, that the specification supports claim 33 drawn to 60 contiguous nucleotides of the polynucleotide of claim 32. Firstly, the claim is rejected due to its dependence on claim 32 which has been rejected for incorporating new matter. Secondly claim 33 recites a polynucleotide comprising at least 60 consecutive nucleotides of the polynucleotide of claim 32. "At least 60" includes polynucleotides which are 60 contiguous nucleotides". Applicant argues that the specification states that "Fragments are those nucleic acids which are greater than 60 nucleotides in length". However, it is evident that the definition in the specification does not encompass fragments which are exactly 60 nucleotides in length, which is a species of the genus encompassed by the claim.

9. The rejection of claims 25, 28, 29, 30, 32, 33, 39 and 41 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. The rejection of claims 44 and 45 is made for the same reasons of record.

Claim 25 is drawn in part to polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to SEQ ID NO:37 Claim 28 specifically embodies the polynucleotide of claim 25 wherein a promoter is operably linked to said polynucleotide. Claim 29 specifically embodies a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn in part to methods of producing polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to SEQ ID NO:37 Claim 32 is drawn in part to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to SEQ ID NO:37, and a complement thereof.

The written description in this case only sets forth polynucleotides encoding SEQ ID NO:37, polynucleotides comprising SEQ ID NO:74, and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acids sequences having 95% sequence identity to SEQ ID NO:37 or polynucleotides comprising a naturally occurring polynucleotide sequences at least 95% identical to SEQ ID NO:74,

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).
The claims are drawn to a genus of variant polynucleotides and neither the common attributes of the genus nor specific examples of species representative of the genus have been described. The structures of naturally occurring polynucleotides having 95% sequence identity to SEQ ID NO:74 and polynucleotides encoding polypeptide having 95% sequence identity to SEQ ID NO:37 are not defined by structure or function and cannot be anticipated from the art.

With the exception of SEQ ID NO:74, and the polynucleotides encoding SEQ ID NO:37, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.
For the reasons set forth above, the specification is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

Applicant argues on page 31 of the response that the statement in the originally filed application that "a naturally occurring expressed polynucleotide sequence at least 95% identical to a expressed polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74" satisfy the written description requirement regarding the possession of the genus of polynucleotides. This is not persuasive. Examination of the specification and the originally filed claims 1-21 indicates that the statement "a naturally occurring expressed polynucleotide sequence at least 95% identical to a expressed polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74" was absent. The quotation supplied by applicant on page 31 that "Thus, the invention contemplates each and every possible variation of nucleotide sequence that could be made in accordance with the standard triplet genetic code as applied to nucleotide sequence of naturally occurring NHRP, and all such variations are to be considered as being specifically disclosed." Clearly the specification contemplated all expressed polynucleotide sequences encoding SEQ ID NO:37 due to the degenerate genetic code. However, the statement of "all such variations" does not provide support for naturally occurring variants having 95% homology to SEQ ID NO:74 or polynucleotides encoding SEQ ID NO:37. It is noted that the quoted statement did not apply the adjective "naturally occurring" to the variants, and further, a specific sequence homology was not suggested. However, even in the event that the statement of naturally occurring expressed polynucleotide sequence at least 95% identical to a expressed polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74 was present in the application as filed this does not entitle applicant to the possession of the genus. Applicant argues that the specification describes variant of SEQ ID NO:37 on page 17, lines 8-16 and page 33, lines 1-5. The textual citation referenced by applicant are only a general discussion of a variant, no specific sequences are described. Applicant alleges that the chemical and structural features of NHRP are described on page 32, lines 24-30. This citation describes only potential glycosylation sites and potential phosphorylation sites within SEQ ID NO:37, the specification does not address the conservation of said glycosylation or phosphorylation sites with the claimed variants or fragments. Applicant argues that one of skill in the art would know how to use the BLAST program to determine 95% identity. That argument is moot because the requirement for written description is not whether one of skill in the art would know how to make and use, but if applicant sufficiently described the claimed invention. Applicant seems to confuse the contemplation of the genus of variants and the genus of polynucleotides encoding fragments and the genus of undefined RNA equivalents with the actual possession of the genus and continually places emphasis on "whatever is now claimed" as stated in Vas-Cath, Inc v Mahurkar (page 31 of the response). The examiner believes that the rejection was on claims which are under consideration, and therefore was indeed what was now claimed. Further, as stated on page 19 of the previous Office action "Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.". Thus, the contemplation of the aforesaid genuses does not constitute an adequate written description.

Applicant argues on page 37 that the instant case differs from previous cases such as Lilly and Fiers because the there is no reliance on a description or functional characteristic of the polypeptides recited in the claims because the instant claims recite structural features. This is not persuasive, the instant claims do not recite structural

features, they recite only sequence homology. This is not the same a structural feature such as a catalytic site or a binding site. Further, the discussion on page 32, lines 24-30 of the predicted glycosylation and phosphorylation sits within SEQ ID NO:37 cannot be construed as to a limitation for the variants and fragments of the encoded polypeptides. Furthermore, no where in the specification or claims as filed, is it stated that the claimed variants or fragments must preserve the glycoslyation sites and phosphorylation sites. Thus, the instant genus claims are not limited by structural features. Applicant argues on page 37 that Brenner et al have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues and that local identity is particularly important in this case for assessing the significance of the alignment. Applicant states that Brenner et al further report that greater or equal to 40% identity over at least 70 residues is reliable in signifying homology between proteins. Applicants reliance of Brenner et al is misplaced as Brenner et al is teaching the identification of evolutionary relationships which differs significantly from a functional relationship or a relation of common use. Further, the citation on page 6076 states that "we learn that 30% identity is a reliable threshold for this database only for sequence alignments of at least 150 residues". On page 6073, second column third full paragraph the database is defined as the "structural Classification of Proteins database which is derived from structural and functional characteristics" . Thus, Brenner is predicting evolutionary relationships within a database of orthologs which are identified independently of sequence comparison. The instant genuses are not limited by functional attributes for the reason set forth above. Thus, reliance on %90 or %95 sequence identity does not guarantee that the variants will have the same functional attributes as SEQ ID NO:37. Further, Brenner et al teach on page 6074, bridging paragraph, that the comparison of structures is more powerful than the comparison of sequences. And that if two proteins show a high degree of similarity in their structural details and function, it is very probable that they have an evolutionary relationship. It is clear that the "function" of a protein cannot be derived solely from sequence information, as recognized by Brenner.

Applicant argues that the state of the art at the time of the present application is further advances than at the time of Lilly and Fiers. This argument is no applicable to the written description requirement because conception is not achieved until reduction to practice has occurred regardless of the ease of isolation of the claimed polynucleotides. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016. Applicant argues that there is simply no requirement that the claims recite particular variant and fragment polypeptide or expressed polynucleotide sequences because the claims already provide sufficient structural definition in claimed subject matter (page 34, second paragraph of the response). This has been considered but not found persuasive. Neither the specification nor claims identify common attributes shared by members of the genus in terms of use or function. Accordingly any expressed polynucleotide having 95% sequence identity to the polynucleotides encoding SEQ ID NO:37 or the expressed polynucleotide of SEQ ID NO:74 would be a member of the genus. Thus the genus is highly varied as it includes polynucleotides having no relationship in terms of function or use to the instant SEQ ID NO:74. Therefore, SEQ ID NO:74 or the expressed polynucleotide encoding SEQ ID NO:37 fails to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus. Thus, applicant was not in possession of the claimed genus.

The specific embodiments of claims 44 and 45 are set forth in the section above. Claim 45 embodies allelic sequences having at least 95 % sequence identity to SEQ ID NO:74. Claim 44 embodies polynucleotides encoding a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:37 encoded by an allele of SEQ ID NO:74 . Thus, the claims are dependent upon allelic sequence of SEQ ID NO:74. It is recognized in the art that an allele is one of tow or more form of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites (Reiger et al, Ed., Glossery of Genetics and Cytogenetics,

1991, page 16). When given the broadest reasonable interpretation, claims 44 and 45 can be interpreted as being drawn to polynucleotides that include naturally occurring mutational sites. The specification does not provide a description of mutation sites that exist in nature within the polynucleotides that encode SEQ ID NO:37 and there is no description of how the structure of SEQ ID NO:74 relates to the structure of any other allele, neural or non-neutral. thus the general knowledge and skill in the art does not provide any indication of how the structure of one allele is representative of unknown alleles. The natures of alleles is that they are variant structures and in the present state of the art the structure of one does not relate to the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of the polynucleotides encoding SEQ ID NO:37 is not representative of the variants of the genus and is therefore insufficient to support the claim.

10. Applicant argues on page 36 that the examiners position is clearly contrary to the USPTOs written description guidelines, published January 5, 2001 which provide that an applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristic which provide evidence that applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical or chemical properties, functional characteristic when coupled with a known or disclosed correlation between function and structure some combination r such characteristics. This has been considered but not found persuasive. By applicants own admission, that the specification has not disclosed a biological significance, function, correlation with a pathological state, or differential expression, of the disclosed polynucleotide. Applicant has adamantly contended that it is not necessary to do so in order to fulfill the utility requirement under 35 USC 101. Thus, the specification does not teach a functional characteristic for the claimed polynucleotide or polypeptide encoded therefore which can be used to correlate with the contemplated variants of the invention

Applicant further quotes the utility guidelines as stating "What is conventional or well-known in the art need not be disclosed in detail if a skilled artisan would have understood the inventor to be in possession of the claimed invention, even if every nuance of the claims is not explicitly described in the specification. This has been considered but not found persuasive.

Claims drawn to variant sequences cannot be even remotely construed to be a "nuance of the claims". A nuance of the claims would be a fusion protein comprising SEQ ID NO:X and a heterologous sequence, wherein it would be expected that the heterologous sequence would not alter the essential properties of SEQ I NO:X. The examiner strongly disagrees that claims drawn to variant sequences can be considered a nuance in a claim. Secondly, without a means to correlate structure with function because SEQ ID NO:74 and the polypeptides encoding SEQ ID NO:37 were not described in terms of function, there is no basis to form a nexus between the variants of the genus and the disclosed sequence. Further, applicant has not described any other member of the claimed genus, with the exception of the degenerate sequences of the polynucleotides encoding SEQ ID NO:37 and thus the disclosed sequences do not describe the claimed genus because the genus is highly variant encompassing members having widely different attributes. Applicant further argues on the bottom of page 36 to the top of page 38 that the claims are sufficiently confined in structure to variants having 95% identity to SEQ ID NO:74. This has been considered but not found persuasive. For the reasons set forth in the written description guidelines quoted above, "An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristic which provide evidence that applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical or chemical properties, functional characteristic when coupled with a known or disclosed correlation between function and structure some combination r such characteristics.". Because it is not possible to make the correlation indicated in the guidelines, because SEQ ID NO:74 or the polypeptide encoded therefrom is itself lacking a function, it logically follows that it is not possible to assign a function to the multitude of variants encompassed by the genus. In any event, the limitations of claims are not limited to a genus with a specific functional attribute, thus the genus of the claims is highly variant and therefore, the disclosure of SEQ ID NO:74 or the polynucleotides encoding SEQ ID NO:37 do not describe the claimed genus, which, when given the broadest reasonable interpretation includes members having highly variant functional attributes .

Applicant argues on page 37 that the claimed polynucleotide variants are defined in terms of SEQ ID NO:74 and the polynucleotides encoding SEQ ID NO:37, and therefore the precise chemical structure of every polynucleotide can be discerned. Applicant concludes that the

examiner's position is nothing more than a misguided attempt to require applicant to unduly limit the scope of the invention. This argument is not persuasive. The claims encompass a genus of polynucleotides and the disclosure of the polynucleotide encoding SEQ ID NO:37 do not adequately describe this genus because the genus is highly variant encompassing a multitude of species having widely different functional attributes.

Applicant states in section 1 of page 37 that because one of skill in the art would know how to use the BLAST program to determine 95% identity, that this indicates that the claimed genus is adequately described. This has been considered but not found persuasive. To reiterate the written description guidelines, "An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristic which provide evidence that applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical or chemical properties, functional characteristic when coupled with a known or disclosed correlation between function and structure some combination r such characteristics". Because the genus encompasses members having widely differing functional attributes, the disclosure of the polynucleotides encoding SEQ ID NO:37 does not describe the claimed genus. Applicant continues to ignore the guidelines and states that "functional limitations are not necessary as the structure and source limitations are sufficient to describe the claimed variant polynucleotides and the claimed polynucleotide encoding variant polypeptides. This is not persuasive in light of the written description requirements which requires, in the absence of a recitation of a representative number of specifies of the genus, a function correlation with the disclosed single member of the genus.

Applicants argue in section 2 that because the claimed variants are not described as having the same function as SEQ ID NO:37 or SEQ ID NO:74 then the examiner's arguments are not relevant to the written description issue. This has been considered but not found persuasive. In the absence of disclosing a representative number of sequences within the claimed genus, a functional correlation must be made with the disclosed single member of the genus in order to limit the genus to those sequences that can b e described by said single member. Applicant argue on the bottom of page 37 to the middle of page 39 that sequence similarity is predictive of functional activity. This argument is irrelevant because the issue is whether or not applicants disclosure is representative of the claimed genus, and for the reasons set forth above,

based on the genus being highly variant,, it is not. Applicant is endowing the claims with limitations that are not set forth.

Applicant has provided the paper by Hegyi et al (Genome Research, 2001, Vol. 11, pp. 1632-1640) to argue that "There is a reasonable probability that the SEQ ID NO:37 polypeptides variants would have the same function as the SEQ ID NO:37 polypeptide". It is noted that on line 11-12 of the abstract it is stated that "In particular, we find that for multidomain proteins, functional can be accurately transferred with only 35% certainty for pair of proteins sharing one structural superfamily". Given this statement, one of skill in the art would conclude that the genus encompassed by the instant claims would reasonably comprise nucleic acids encoding proteins having different functional attributes than the instant SEQ ID NO:74 which encodes a protein of unknown attributes, because the genus has a significant probability of including proteins not sharing the same function.. Further, arguments that there is a certain probability of the genus comprising polynucleotide with the same functional attributes as SEQ ID NO:74 are not convincing. Even if the genus encompasses a single member having a widely different function from SEQ ID NO:74 it would be concluded that the disclosure of SEQ ID NO:74 does not adequately describe the claimed genus. Applicant again presents the argument that because Brenner teaches that a 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that a greater than 40% identity over at least 70 residues is reliable for signifying homology between two proteins, the genus of polypeptides at least 95% identical to SEQ ID NO:37 would more likely than not functional similarly to the polypeptide of SEQ ID NO:37 is again not persuasive. Applicants reliance of Brenner et al is misplaced as Brenner et al is teaching the identification of evolutionary relationships which differs significantly from a functional relationship or a relation of common use. Further, the citation on page 6076 states that "we learn that 30% identity is a reliable threshold for this database only for sequence alignments of at least 150 residues". On page 6073, second column third full paragraph the database is defined as the "structural Classification of Proteins database which is derived from structural and functional characteristics". Thus, Brenner is predicting evolutionary relationships within a database of orthologs which are identified independently of sequence comparison. The instant genuses are not limited by functional attributes for the reason set forth above. Thus, reliance on 90% or 95%

sequence identity does not guarantee that the variants will have the same functional attributes as SEQ ID NO:37. Further, Brenner et al teach on page 6074, bridging paragraph, that the comparison of structures is more powerful than the comparison of sequences, and that if two proteins show a high degree of similarity in their structural details and function, it is very probable that they have an evolutionary relationship. It is clear that the "function" of a protein cannot be derived solely from sequence information, as recognized by Brenner. Further, arguments that the claimed polypeptides have a probability of having the same function as SEQ ID NO:74 or the polynucleotide encoding SEQ ID NO:37 are moot because if the genus includes even one member with different functional attributes then it flows logically that the disclosure of the polynucleotides encoding SEQ ID NO:37 cannot adequately describe the claim genus.

Applicant argues in point 4 on page 39 that the primary structure of the claimed protein is completely described by the amino acid sequence and because claim 25 limits the structure of the polypeptides encoded by the claimed polynucleotide to those naturally occurring amino acids at least 95% identical to SEQ ID NO:37 and that this limitation conserves the function of the polypeptides encoded by the claimed polynucleotides. It will be pointed out that the cited Stryer reference also teaches secondary and tertiary structure which allows the polypeptide to form a three dimensional shape and thus a domain. The claims are not limited to polynucleotides encoding polypeptides having the same three dimensional structure or domains of SEQ ID NO:37 and further, as stated above, if the genus includes even one member with different functional attributes then it flows logically that the disclosure of the polynucleotides encoding SEQ ID NO:37 cannot adequately describe the claimed genus. Applicant further argues on the top of page 40 that "the examine alleges that here is no limitation in the specification as to the conservation of glycosylation and phosphorylation sites between SEQ ID NO:37". Applicant refers the examiner "to the claims". This has been considered but not found persuasive. Neither the claims not the specification dictate that the claimed variant polynucleotides encode polypeptides which conserve the same glycosylation and phosphorylation sites that were predicted for SEQ ID NO:37.

Applicant argues in the middle of page 40 that the claimed polynucleotides share the structural attributes of sequence identity and because they are "naturally occurring, share a

common use in toxicology testing. This has been considered but not found persuasive. Applicant has not limited the genus of claimed polynucleotide to those having the same functional attributes of SEQ ID NO:74 of the polynucleotides encoding SEQ ID NO:37, thus, the disclosure of the polynucleotides encoding SEQ ID NO:37 fails to describe the claimed genus. Applicants comment that the claimed polynucleotide are naturally occurring and thus share a "common use" in toxicology testing does not suffice to limiting the claimed genus to the same attributes as the disclosed polynucleotide or the polypeptide encoded therefrom.

11. The provisional rejection of claims 25, 28, 29, 30, 32, 33, 39, 41 and 42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 7 of copending Application No. 09/539,800 is maintained. Acknowledgment is made of applicants intention to file a terminal disclaimer until such time as there is an indication of allowable subject matter.

12. All other rejections and objections as set forth in Paper No. 12 are withdrawn in light of applicants amendments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/27/03